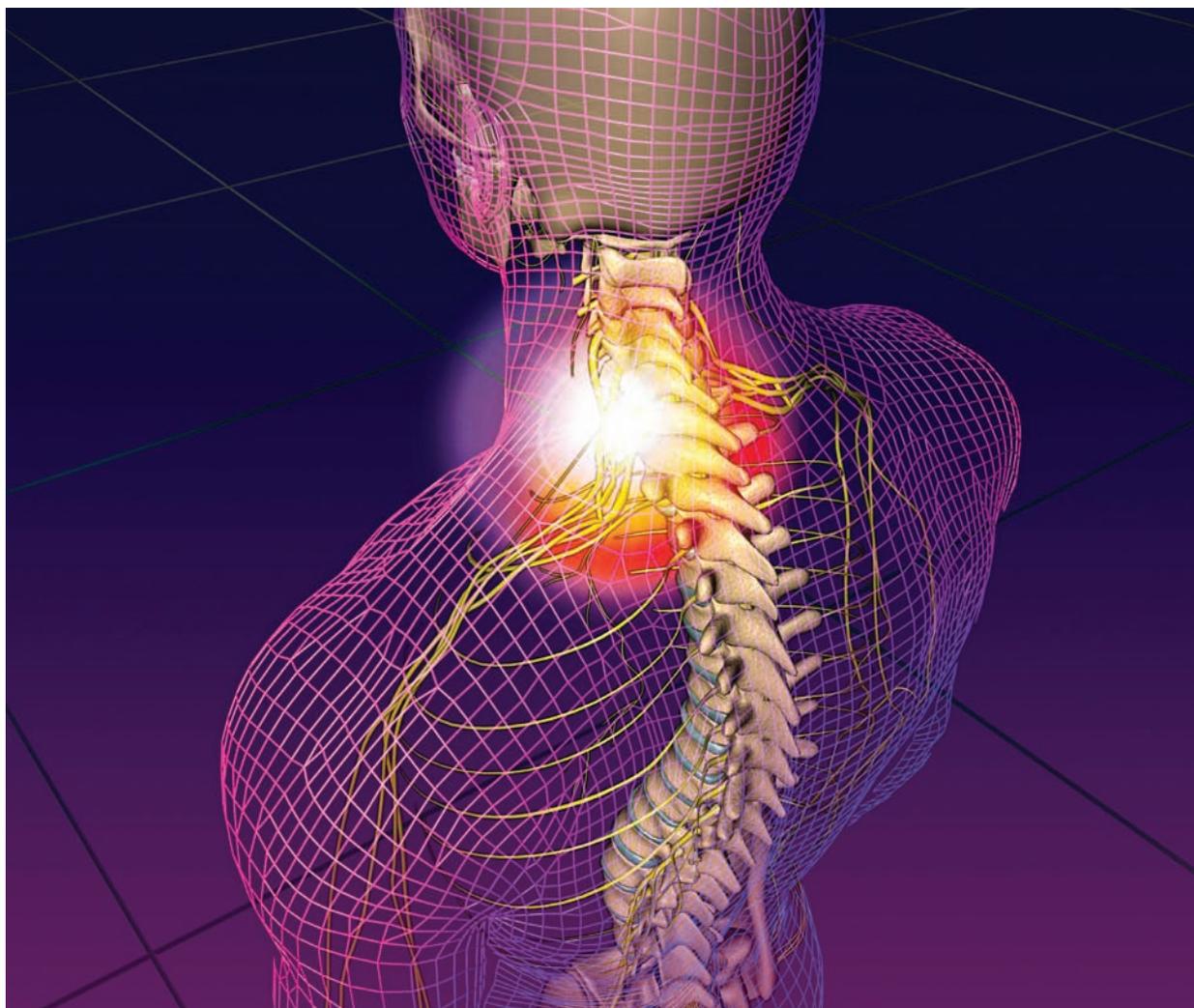


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DISEASE STATE GUIDE

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PAIN

Overview of Mechanisms and Management



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PAIN

Overview of Mechanisms and Management

Pain is defined as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*¹ The experience of pain is familiar to everyone; however, the intensity, character, and tolerability of each person's pain is subjective. Even with the same stimulus (eg, surgery or arthritis), one patient may feel intense burning pain that cannot be ignored while another may experience dull throbbing that interferes only with sleep. How patients perceive and react to pain is influenced by social, cultural, and psychological factors.² Thus, healthcare professionals must rely on each patient's description of his or her pain in order to recommend appropriate treatment.³ Detailed examination as to the kind and intensity of pain, how and when it occurs, and the effects of pain on daily activities is needed.⁴

Upon examination, patients may describe pain as mild or severe, constant or episodic, localized or widespread, numbing or tingling, throbbing or piercing, dull or sharp, and, finally, tolerable or intolerable.² Standardized pain scales are used to measure the severity and tolerability of patients' pain by applying a number or a visual clue to the extent of discomfort (FIGURE 1). These tools allow comparisons of pain severity over time and evaluation of pain therapy when used sequentially for the same patient.^{4,5}

Acute pain is often defined as *pain that comes on quickly and usually as the result of a known injury or noxious stimulus.* In general, acute pain is expected to last a relatively short time (hours, days, or weeks) and to resolve as the tissue heals.⁴ Postoperative pain and pain immediately following an injury are clinical models of acute pain.

In contrast, chronic pain lasts for at least 3 months or even as long as a lifetime. Osteoarthritis, diabetic peripheral neuropathy, or cancer are common causes of chronic pain.⁴ In addition, pain that was originally caused by an injury (for example, low back pain) or surgery but lasted longer than the healing process is considered chronic pain.⁴

Diagnosis and adequate treatment of pain may be hindered by patients' reticence to discuss pain and concerns about pain medications.⁶ A study of patients with cancer-associated pain examined several areas of concern that could affect whether patients followed treatment recommendations or inhibit reporting of the severity of pain to physicians. Regarding opioid treatment recommendations, some patients had specific beliefs that they would become addicted to analgesics or tolerant to the effects of opioids so that they would not work when the pain became worse. Also, many had concerns about the side effects of opioids, especially nausea (endorsed by 83% of patients) and constipation (endorsed by 85%), and fear of injections associated with the administration of some opioid medications.⁶

Further, patients reported that they might not complain of the severity or increases in their pain because of a fatalistic attitude that pain is inevitable with their condition, or because they worried that increasing pain signified progression of their disease. Some believed that physicians would be distracted from treating the illness if they complained or annoyed the physician by discussions of pain.⁶

Incidence and impact

Pain is a leading cause of reduced quality of life and disability in the United States.⁴ Recent problems with

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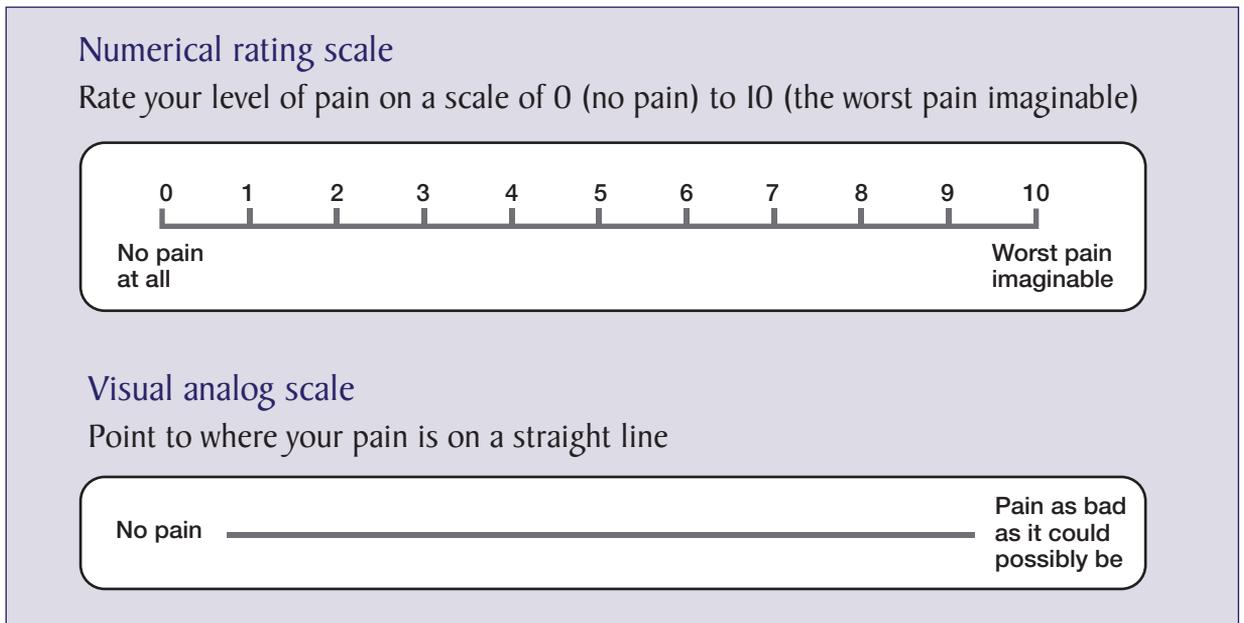


Figure 1. Tools that may be used to measure pain intensity in the clinic.

pain that had lasted more than 24 hours was reported by as many as 26%, or more than 76 million American adults age 20 years and older, in the 1999-2002 National Health Examination Survey.⁷ Among those who reported pain, 32% said it had lasted less than 1 month and 42% reported that pain had lasted more than 1 year.²

Notably, as many as 27% of individuals in the survey said they had experienced significant low back pain lasting 1 day or more in the 3 months before the interview. This percentage was fairly consistent across age and gender groups (TABLE 1).² Adults who said they recently had low back pain lasting more than 24 hours also reported worse health status than those who did not, regardless of age. Twenty-eight percent of those with recent low back pain had some activity limitation, compared with 10% of those who did not report low back pain; individuals with recent low back pain reported fair or poor overall health status about three times more often than those without low back pain. Individuals with recent low back pain lasting more than 24 hours were four times more likely to be identified as having severe psychological distress.²

Acute and chronic pain are associated with significant losses in productivity at

work and at home, as well as increases in healthcare costs that are attributed to extended hospital stays and unexpected emergency room and clinic visits.⁴ Again, low back pain is a notable example: it is the most common cause of job-related disability and a major contributor to missed work. Americans are calculated to spend as much as \$50 billion annually related to low back pain.⁸

Inadequate management of acute pain (pain associated with a specific stimulus that has lasted less than 3 months) may result in serious and long-term consequences for patients. Physiologic stress responses caused by activation of the autonomic nervous system may lead to changes

Table 1. Adults Reporting Low Back Pain Lasting 1 Day or More and Not Considered Minor

Age	Total (% ± SE)	Men (% ± SE)	Women (% ± SE)
18 years and older	27.2 ± 0.3	25.0 ± 0.5	29.2 ± 0.4
18-44 years	23.9 ± 0.5	22.0 ± 0.6	25.8 ± 0.6
45-64 years	30.8 ± 0.5	28.9 ± 0.8	32.5 ± 0.7
65 years and older	30.4 ± 0.7	27.2 ± 1.1	32.8 ± 0.9

SE: Standard error. Source: Reference 2.

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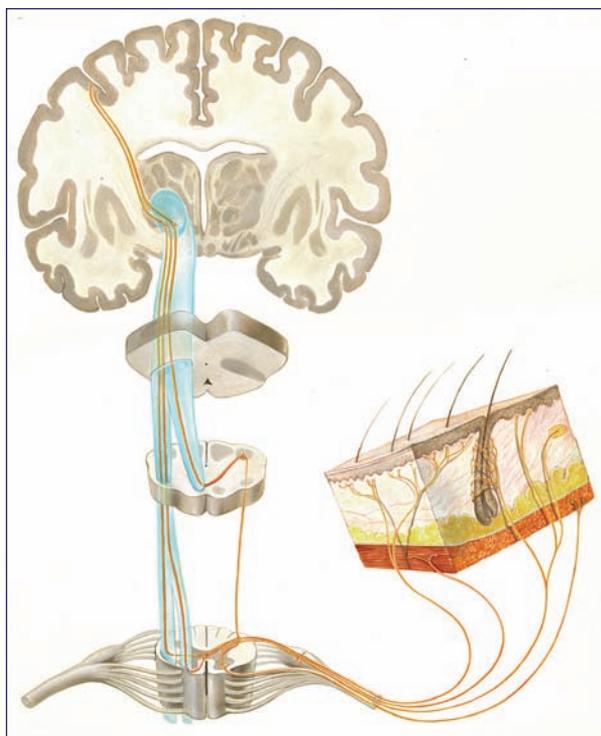


Figure 2. Stimulation of pain receptors in the skin sends a pain impulse up a sensory nerve to the spinal ganglion. The impulse crosses over the spinothalamic tract and the reticular formation, and then through the thalamus to the sensory cortex of the brain.

in the cardiovascular system, such as increased heart rate and arterial blood pressure, which could lead to myocardial ischemia and infarction in some patients.⁹ Effects on gastrointestinal secretions and intestinal motility may be associated with ileus, nausea, and vomiting.⁹ Impaired immune function affects some patients with pain, which may increase the potential for infection and tumor spread.⁹ Psychological problems, such as fear, anxiety, and depression, and increased physical disability with loss of mobility may also result from ineffective management of acute pain.⁹ Finally, unresolved acute pain may become chronic (lasting longer than 3 months) and increase patients' distress and disability for long periods of time.^{9,10} These problems result in high hospitalization rates, delayed recovery and return to normal activities, and high healthcare costs.

Mechanisms of Pain

Two common types of pain are the result of interactions between neuroanatomic pathways that are important in

the experience of pain and in relief of pain. *Nociceptive* pain is the normal physiological response to a noxious stimulus, such as an injury or inflammation. The noxious stimulus is detected by free nerve endings (nociceptors) and causes release of neurotransmitters from the nociceptor, such as glutamate, substance P, and calcitonin gene-related peptide, which activate second-order neurons in the spinal cord. The second-order neuron travels up the spinothalamic tract that leads to the thalamus, where it synapses with the third-order neuron that projects to the sensory cortex, where the pain is perceived (FIGURE 2).¹¹

Continuous stimulation of nociceptors may result in repetitive firing of the nociceptor and a decrease in the threshold for firing, or "sensitization" of the nociceptor. In addition, continued release of neurotransmitters from the original responding nociceptors may cause recruitment of previously "silent" nociceptors and additional pain (*hyperalgesia*), as well as peripheral changes associated with pain, such as redness, swelling, and tenderness. *Allodynia*, or pain caused by normally non-noxious stimuli, may also be caused by these mechanisms.¹¹ Second-order neurons may also become sensitized by continuous stimulation (as in the case of an injury) and contribute to hyperalgesia and allodynia.

What Does a Doctor Need to Know About Patients' Pain?

The following are questions healthcare professionals may ask about pain.

- On a scale of 1 to 10, how intense would you say your pain is?
- Where do you feel the pain?
- What does it feel like (stabbing, burning, tingling)?
- How long have you had the pain? Has it gotten better or worse over time?
- How does the pain affect your daily activities?
- What helps relieve the pain and what makes it worse?
- Have you tried OTC pain medications like aspirin?
- Have you tried heat or ice to relieve the pain?
- Have you seen other physicians about pain? Did they prescribe any treatments?
- What medications are you taking now for pain?
- Have your pain medications caused any side effects that would keep you from taking them?

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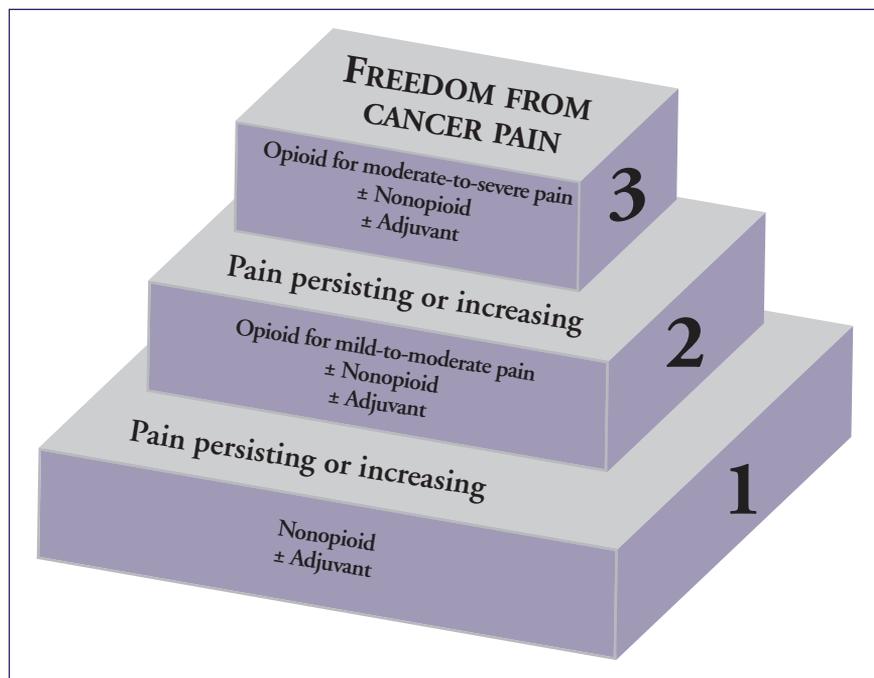


Figure 3. World Health Organization's three-step "ladder" for cancer pain relief.

This decrease in the threshold for activation in the spinal cord is called "central sensitization."¹¹

Pain signals are modulated by the supraspinal release of endorphins and enkephalins. These neurotransmitters interact with specific opioid receptors in descending modulatory neurons that synapse with the primary or afferent neuron, the second-order pain transmission neuron, or interneuron. These descending neurons release norepinephrine and serotonin, which directly inhibit the release of pain transmitters from the incoming afferent signal and inhibit the activity of the second-order pain transmission neurons.¹¹ Studies have demonstrated that dual-action selective serotonin and norepinephrine reuptake inhibitors may have significant effects on pain relief.¹²

Neuropathic pain is the result of loss of the inhibitory activities of the descending pathway on pain transmission (disinhibition). Lesions of the dorsal horn of the spinal cord, spinothalamic tract, thalamus, and/or cerebral cortex may also produce neuropathic pain in patients with central pain.¹³ In addition, nerve injury may activate descending "facilitatory" neurons that produce a continuously sensitized state of the spinal cord.¹³ Persistent pain may be maintained by remodeling (neuroplasticity) of the central nervous system.^{11,14}

Current Strategies for Pain Management

The source, location, description, tolerability, kind (acute or chronic), category (nociceptive or neuropathic), and intensity of pain are important determinants of which class of medication therapy may be recommended for pain relief. A thorough examination is needed to determine physical and psychosocial effects of the pain on the patient's activities and relationships. Based on these findings, physicians may recommend pharmacological and nonpharmacologic therapies for pain. Potential nonpharmacologic interventions, such as counseling and relaxation techniques, physical

rehabilitation, and complementary or alternative medicine practices. A number of organizations offer resources for patients and healthcare practitioners who consider these treatment options.¹⁵

Pharmacological therapies for pain fall into three broad categories. *Nonopioid* and *opioid* analgesics have specific analgesic qualities and are indicated for acute or chronic pain. *Adjuvant* medications include several classes of drugs with mechanisms that affect pain and pain relief pathways, such as certain antidepressants and anticonvulsants. The group of adjuvant medications may also contain drugs with no analgesic qualities but with utility in overall management of pain syndromes, such as those for insomnia, anxiety, depression, and muscle spasms.¹⁵

Nonopioid analgesics include the nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, and acetaminophen. NSAIDs reduce the production of prostaglandins that increase pain signalling at the site of pain.¹⁵ NSAIDs are effective for mild to moderate pain and for acute and chronic types of pain.¹⁵ Acetaminophen is also recommended for mild to moderate pain; however, long-term use with large doses carries a risk of liver damage.¹⁵

Opioid analgesics, such as codeine and morphine, are effective for moderate to severe acute pain, such as post-

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operative pain or injury.¹⁵ Opioids are also often recommended according to the World Health Organization pain ladder for relief of moderate to severe chronic pain related to cancer and persistent mild to moderate pain not associated with cancer (FIGURE 3).^{16,17} Opioids mimic the actions of endorphins. In addition to pain relief, opioids may improve psychological coping and toleration of pain.¹⁵

As previously mentioned, antidepressants that inhibit serotonin and norepinephrine reuptake, such as tricyclic antidepressants and selective reuptake inhibitors, are known to produce analgesia for some patients, especially those with neuropathic pain.¹³ In general, those that inhibit reuptake of only norepinephrine (norepinephrine reuptake inhibitors; NRIs) or both neurotransmitters (serotonin/norepinephrine reuptake inhibitors; SNRIs) have been found more effective for the management of pain than those that affect serotonin reuptake only (SSRIs).¹² These effects occur whether or not pain is associated with depression.¹² In conjunction with the potential for functional interactions between opioid and norepinephrine receptors these data suggest that norepinephrine activities have an important role in development of analgesia.¹³

The anticonvulsant medications gabapentin and pregabalin may be effective for some patients with neuropathic pain.¹⁸ These compounds inhibit neurotransmit-

ter release by binding to voltage-gated calcium channels of central nervous system tissues and are indicated for neuropathic pain syndromes as well as for epileptic seizure control.^{16,19,20} Topical lidocaine may also be recommended for localized neuropathic pain.¹⁸ Finally, corticosteroids may be useful for pain caused by inflammatory states and muscle relaxants may be useful for pain caused by muscle injury or muscle spasms.¹⁵

Increased understanding of mechanisms of pain has focused attention on targeting the neurobiologic mechanisms at work in individual patients with pain.²¹

Although analgesics are labeled according to efficacy for acute or chronic pain and mild to severe pain intensity, not all pain in any one category is associated consistently with the same mechanisms of pain.²¹

Conclusion

Noiceptive and neuropathic pain arise from complex interactions between neurological pathways in the spinal cord and brain. Modulation of both ascending and descending pathways that are involved in transmission and inhibition of pain signalling may provide effective analgesia for many patients. In particular, clinical evidence suggests that therapy that engages the actions of norepinephrine may be an important treatment option for pain. ♦

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Pain is a familiar experience to every person. However, many people have pain that is so intense or distressing that it cannot be ignored and activities of daily life become difficult or impossible. Pain may arise from obvious sources, such as injury, surgery, or disease—or the cause of pain may not be known to the patient or to the physician. For these reasons, the patient's perceptions of the intensity and tolerability of pain are important to healthcare professionals for determining appropriate therapy.

Descriptions of Pain

Healthcare professionals need to know the intensity, nature, and effects of patients' pain. Pain scales, which allow patients to rate the severity or intensity of pain on a numerical or visual scale, are often used. In addition, the pain may be described as burning, stabbing, tingling, numbing, or dull. The circumstances that increase pain, such as lying down or movement, are also important.

Pain is described as *acute* (pain associated with a noxious stimulus and having lasted for less than 3 months) and *chronic* (having lasted for more than 3 months). Acute pain tends to resolve as the injury heals, while chronic pain is not necessarily associated with the original stimulus. These distinctions may affect which medications are prescribed. Treatment of acute pain, regardless of intensity, is important to prevent the pain from having adverse effects on the cardiovascular, gastrointestinal, and immune systems through activation of the autonomic nervous system. In addition, unresolved acute pain may lead to anxiety, depression, and other psychosocial problems for the patient. Finally, acute pain may cause remodeling of neurological pathways so that pain becomes chronic and has adverse effects on patients' lives for months or years.

Healthcare professionals also need to be aware of potential barriers that may keep patients from talking about pain or pain therapies, with significant effects on their comfort and quality of life. These barriers include worries about the implications of their pain (eg, a serious or worsening medical condition). Patients may also have specific concerns about taking pain medications, especially those related to addiction and side effects. Counseling about addiction and side effects

and instructions about how to minimize the possibility of these events may provide reassurance. In addition, many patients have low expectations of the efficacy of pain medications because of previous experiences. Careful questioning about pain interventions that patients have already taken and whether they were effective may be helpful to elicit these concerns.

Pain Medications

There are three broad categories of pain medications that may be prescribed. Nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are generally used for mild to moderate pain. Many of these are available over the counter and some are used in combination with the other category of pain medication, opioid analgesics. Opioids are indicated for moderate to severe pain and are controlled substances, available only by prescription. These drugs interact with opioid receptors in the brain and spinal cord and mimic one of the body's natural responses to pain.

Adjuvant pain therapy includes several types of medication that may have specific analgesic activity, or do not produce analgesia but are useful in the overall management of pain. Antidepressants in the serotonin/norepinephrine reuptake inhibitor (SNRI) class are often prescribed for patients with long-lasting pain, whether or not the patient is diagnosed with depression. These therapies inhibit pain signaling and are effective for some patients. Patients and caregivers should be informed about the potential for mood and behavioral side effects associated with these therapies. In addition, the anticonvulsants gabapentin and pregabalin have been shown to be effective for

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some patients with neuropathic pain.

Patients may be advised that, because of several different mechanisms involved in pain, a particular pain medication may not work for every person or every kind of pain. For this reason, different types of therapy may be used concurrently, or trials of different pain medications may be needed.

Nonpharmacologic Treatments for Pain

Physicians may recommend psychosocial interventions to help patients understand their pain and reduce stressors that can worsen pain or its effect on their lives. These interventions may include behavioral health testing and counseling to determine the coping mechanisms used by the patient and whether they are helpful or harmful. Individual and/or group counseling and specific techniques, such as relaxation therapy, biofeedback training, hypnotherapy, behavior modification, and stress management training, may be very helpful for the patient and his or her family.

In addition, physical rehabilitation may be recommended to correct or decrease the effects of physical

problems that are associated with pain. Psychiatrists, physical therapists, occupational therapists, and exercise physiologists have specialized training in rehabilitation techniques that may be helpful for some patients who have pain. Some complementary and alternative techniques, such as acupuncture, mind-body therapies, yoga, and massage, are considered helpful additions to other types of pain therapy by many patients and physicians. Finally, interventions such as surgery, implantable devices, neuroablation, and infusion therapies may be needed for some patients with chronic or persistent pain that is not responsive to noninvasive treatments.

Other Resources

Unresolved pain increases distress and disability for large numbers of individuals in the United States. Many resources are available to help patients with pain understand their condition and become aware of pharmacologic and nonpharmacologic treatment options and sources of support. The organizations listed at the end of this guide provide information that may prove useful for patients and healthcare professionals. ♦

Resources

The following organizations provide additional information about pain treatment options and resources for patients and healthcare professionals.

American Academy of Pain Management

www.aapainmanage.org

American Academy of Pain Medicine

www.painmed.org

American Pain Society

<http://ampainsoc.org>

American Chronic Pain Association

<http://theacpa.org>

American Pain Foundation

www.painfoundation.org

The National Foundation for the Treatment of Pain

www.paincare.org

Pain Treatment Topics

<http://pain-topics.org>

Counseling Corner

The following series of questions and answers serves as a patient education aid to assist healthcare professionals in counseling patients who are receiving pain medications.

Q. How does this medication work for my pain?

A. Pain medications work by interfering with the neurological signals between the site where the injury has occurred and the brain. Agents like aspirin and ibuprofen help reduce inflammation as well, which may be the source of some of the pain. Opioid medications interact with specific receptors in the sensory nervous system and activate the body's natural pain-relieving mechanisms, so that the pain signals coming from the injury are inhibited. Antidepressants also enhance the activity of natural pain inhibitory pathways to provide pain relief for many patients.

Q. Why is it important to treat the pain specifically, even if the injury is healing?

A. Pain that is prolonged for too long can have many adverse effects on the body, because it activates other parts of the nervous system than those affected by the injury. For example, some patients may have a stress response to untreated pain that results in cardiovascular and gastrointestinal effects. Also, untreated pain may last for weeks or months, even after the injury has healed, and in some cases the pain may be permanent.

Q. How long will it take for this medication to work?

A. Some medications need to build up in the body to have maximum effect. The dose of some medications may also be increased over time to allow the body to become adapted and reduce side effects. Healthcare professionals should be notified if side effects are too bothersome during the initial treatment period so they can recommend dose adjustments or other treatments.

Q. Can I become addicted to my opioid pain reliever?

A. Addiction is usually not a problem for patients who have no history of substance abuse and take their medications as directed by the physician. Addiction means that the patient cannot control his/her use of the medication, regardless of the consequences to himself or others.

Addiction is not the same thing as physical dependence, which may occur with opioid medications and other classes of drugs. In this case, suddenly stopping the medication may cause uncomfortable symptoms. If this withdrawal effect is known to be associated with a particular drug, the physician may advise slowly tapering down the dose of the drug when the drug is no longer needed for pain. Patients should contact a healthcare professional before starting or stopping any pain medication.

Q. How does my physician know how much pain medication I should take?

A. The patient is the best source of information about the intensity of pain and how much the pain interferes with his or her life. The physician needs to know how and when the pain occurs and whether any prior therapies were effective. Patients with chronic or severe pain that is not getting better may benefit from consultation with physicians who are specialists in pain.

Q. What are some terms that I could use to describe my pain?

A. The descriptions of pain, can vary widely from person to person, even if the pain is caused by the

Counseling Corner

same problem (ie, arthritis or surgery). Here are some terms that may be used: dull, sharp, throbbing, piercing, numbing, tingling, localized, widespread, burning, shooting, electric, mild, moderate, severe.

Q. What should I do about side effects from my medication?

A. Many options are available for lessening side effects associated with pain medications. Patients should tell their physicians about side effects and how severe they are. Physicians may adjust the prescribed dose or recommend taking other medications to counteract specific side effects. If the side effects are not tolerable, switching to a different medication may be necessary.

Q. Why did my physician recommend counseling?

A. Counseling and some nondrug therapies like relaxation therapy, stress management training, behavioral therapy, or hypnotherapy may help some patients gain more control over their pain and its effects on their lives. These techniques may provide better coping mechanisms for the patient and are often used in conjunction with drug therapy.

Q. What else can I do for pain?

A. Physical rehabilitation specialists may help with different kinds of physical therapy, occupational therapy, or specific exercise programs. In addition, various kinds of complementary and alternative medicine techniques may be helpful for some patients. These kinds of therapy should be undertaken with the advice of a physician. Surgery, infusion therapy, and implantable devices may also help relieve some kinds of chronic pain. ♦

Notes

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